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UK VACCINE CAPACITY

Annual seasonal influenza outbreaks and pandemic disease planning have generated parliamentary interest about the UK's position in sourcing adequate quantities of vaccines.[1] A key policy issue concerns the extent to which the government should stimulate vaccine research and manufacturing capacity rather than it being led by the commercial interests of the pharmaceutical sector. This POSTnote gives an overview of the position in the UK and how public health interests are reconciled with those of industry.

Background

Vaccines stimulate the immune system to respond to disease-causing micro-organisms (such as bacteria or viruses). They are the most cost-effective health treatment and are used to:

- **prevent disease** - giving healthy people vaccines allows them to build immunity to a disease without being exposed to it. Most of the vaccines currently routinely given in the UK prevent diseases such as diphtheria, tetanus, measles, mumps and meningitis. Globally, the World Health Organisation estimates that vaccines prevent 2 million deaths every year.[2]
- **treat existing disease** - therapeutic vaccines, which stimulate the immune system to fight existing disease, as well as preventing future infection are also in development. Promising targets include type 1 diabetes, multiple sclerosis, rheumatoid arthritis and some cancers.

UK vaccine policy

The Department of Health (DH) sets national policies outlining which vaccines will be used in what populations (Box 1). Policies cover UK-wide childhood and other immunisation programmes, such as seasonal influenza vaccination. The DH commissions and funds a limited amount of research. This tends to focus on later stages of vaccine development and their relevance to UK health needs, and provides an evidence base to inform policy decisions for national immunisation programmes.

Box 1. UK national immunisation programmes

Childhood immunisation

The national programme schedules 12 separate injections in various combinations against 10 infectious diseases before the age of five. The same immunisation programme is used year on year in successive birth cohorts (subject to policy changes).

Seasonal influenza and pandemic disease

Planning vaccination against possible pandemic disease (such as influenza) or for annual seasonal influenza presents a different set of challenges. Seasonal influenza infections typically start in the winter, so the DH begins planning and discussing its requirements with the vaccine industry in the spring. The main challenge for industry is to develop, manufacture and test vaccines for the relevant influenza strains in time and in sufficient quantities to curtail the spread of disease. The DH planning process to manage possible pandemics includes estimating vaccine requirements (where they are available) and providing manufacturers with forecasts of national needs.

The Health Protection Agency (HPA) monitors trends in infectious disease and runs the National Vaccine Evaluation Consortium. This group undertakes clinical evaluations and vaccine safety research as well as economic modelling and evaluation of new immunisation programmes to inform DH policy decisions. An independent expert body, the Joint Committee on Vaccination and Immunisation (JCVI) advises the DH on the scientific aspects of vaccination. It includes experts from a wide range of relevant subjects who consider industry developments, scientific evidence, international immunisation schedules and research when recommending new vaccines or immunisation schedules. The JCVI also 'horizon-scans' to look at longer-term prospects in vaccine research and development. The vaccine industry is not formally involved in this process.

The DH is the largest purchaser of vaccines in Europe, spending ~£200m every year on centralised purchase and distribution for national immunisation programmes. It costs ~£200 to vaccinate a child fully according to the

routine schedule. The DH spend on vaccines will increase considerably when the recently licensed human papilloma virus (HPV) vaccination against cervical cancer is introduced for teenage girls in autumn 2008.

The vaccine industry

The major commercial vaccine manufacturers are usually divisions of large multinational pharmaceuticals, limited to a few suppliers. While the industry is a global business and manufacturing facilities are not tied to the country of sale, many companies have operations based in Europe. The number of new vaccines coming onto the market is increasing, although the number of companies producing them has decreased in recent years, due to withdrawal from vaccine research or company mergers.[3] Overall, only a handful of vaccine companies supply the DH immunisation programme.

Developing new vaccines

It can take ten years or more to research, develop and assess the efficacy and safety of a vaccine before it can be given to people. There are examples where this has been done more quickly: a meningococcal C vaccine was available within five years. To ensure safety, stringent EU and UK regulatory procedures apply: the vaccine, the manufacturing facility and the production process must all be licensed prior to marketing (Box 2). Data on vaccine research and development are collated by trade bodies (which are not involved in licensing medicines), the Association of the British Pharmaceutical Industry (ABPI) and the UK Vaccine Industry Group (UVIG).[4] Several vaccines have recently been licensed, with many more in clinical development (Box 3).

Box 2. Regulatory approval of vaccines

The European Medicines Agency (EMEA) considers the efficacy and safety of vaccines and issues EU-wide marketing authorisations (licences). Regulation of vaccines also includes the licensing of the production process and the manufacturing facility.

Post-marketing surveillance is undertaken by the EMEA, UK government bodies, manufacturers and academia. This includes estimating the incidence of disease in the vaccinated population (and thus the level of immunity) as well as recording adverse outcomes. In the UK, surveillance of vaccine efficacy, quality, safety and take up is monitored by the Medicines and Healthcare products Regulatory Agency (MHRA) and the HPA. The EMEA and MHRA may revoke a licence if new information changes the original risk-benefit assessment.

For many biological products including vaccines, the quality and efficacy of each batch must be tested and approved before release onto the market. Testing is done by:

- the vaccine manufacturer themselves;
- one of several independent European Official Medicines Control Laboratories. The UK has one of the major independent quality assurance testing facilities, the National Institute for Biological Standards and Control.

Setting priorities: developing new vaccines

Economic considerations

Like any other medicine, the costs of vaccine research, development and regulatory approval are considerable. Therefore, a company has to be confident that it is scientifically possible to make a vaccine and that there is a reasonable sized market for its product to be profitable. Economic factors also mean that companies are less likely to develop vaccines for rare diseases or those endemic to the developing world such as malaria and HIV, without government initiatives or other incentives such as tax credits or advance market purchase commitments. Similar considerations mean that industry is unlikely to develop vaccines on a speculative basis against potential threats, such as bioterrorist agents or emerging diseases.[5]

The technical and commercial features of the vaccine market mean that companies tend to seek global markets for each vaccine. This increases the chance a company will recoup its development costs and make a profit. This may mean that some specific national requirements may not be supplied. For example, a new combination paediatric vaccine that would suit a complex European childhood immunisation programme may be inappropriate for a developing country where different (usually younger) ages at vaccination are needed. Developing countries may access vaccines through companies' tiered pricing schemes and initiatives such as the Global Alliance for Vaccines and Immunisation.

Box 3. Current vaccine research and development

Vaccines licensed recently

- human papilloma virus (cervical cancer)
- rotavirus (a common cause of diarrhoea in children);
- varicella (chickenpox);
- influenza (H5N1 strain);
- pneumococcal vaccine for infants.

Vaccines in late stage clinical development

- numerous combination vaccines;
- genital herpes;
- Japanese encephalitis.

Vaccines in early stages of development

- streptococcus group A and B;
- pathogens causing food poisoning including *E. coli* and *Salmonella*;
- hepatitis C;
- bacteria (*H. pylori*) implicated in stomach cancer and gastric ulcers;
- respiratory syncytial virus (serious childhood infection);
- chlamydia and herpes (sexually transmitted infections);
- several other vaccines relevant to the developing world, including cholera, TB, typhoid, West Nile virus and HIV.

Public health considerations

The Chief Medical Officer's most recent national strategy to tackle infectious disease was published in 2002.[6] This outlined future priorities for immunisation including plans to consider using the then newly available vaccines (varicella {for chicken pox} and pneumococcus) as well as stimulating research and investment to develop new vaccines for common and/or serious vaccine-preventable infections:

- meningococcus group B;
- respiratory syncitial virus (a common cause of chest infection and hospital admission);
- rotavirus gastroenteritis.

While the DH monitors the burden of infectious disease, there is no formal framework in the UK to reconcile

public health priorities with those of the vaccine industry. The DH engages with the international vaccine community (scientists and policymakers), and with vaccine manufacturers, through the UVIG or individual companies. The industry welcomes dialogue with the government since information about DH priorities can inform decisions about where to invest in commercial vaccine development. For example, the DH had an early dialogue with industry to reduce the commercial uncertainties associated with developing a meningitis C vaccine (introduced in the UK in 1999). The industry would welcome an update of the Government's 2002 infectious disease strategy which would give a clear indication of national health (and vaccination) priorities.

Government and the vaccine industry

A tension exists between the need to control public expenditure on vaccines and the government's responsibility to encourage investment in research and development. In a market with few suppliers, the government is keen to encourage an innovative and competitive vaccine industry with several sources of supply for any given vaccine. However some argue that the influence of governments as major buyers has effectively limited the profit margins of the industry and reduced the number of suppliers (see Box 4.)

Box 4. Vaccine purchase and pricing

EU public procurement legislation requires that vaccine contracts encourage sufficient competition and that tenders are evaluated fairly. The JCVI has no powers to decide which company's vaccines will be purchased and it is not involved in the procurement process. Neither does it make recommendations on using a particular vaccine if there are multiple manufacturers. The DH invites tenders for vaccine contracts stipulating desirable criteria that the vaccine should satisfy: safety, efficacy, availability and price. Some industry experts view the purchasing practices as a form of controlled pricing.

Vaccines are included in the main drug pricing negotiations between the ABPI and the government. The Pharmaceutical Price Regulation Scheme indirectly controls the prices of branded medicines by regulating the profits that companies can make on NHS sales. Companies receive allowances for UK research and development activities. This ensures that the NHS obtains medicines at reasonable prices.

As it is essentially a single buyer, the government can use its position to negotiate vaccine price reductions and other advantageous contractual conditions. One consequence of the downward pressure on prices means that older vaccines tend to cost considerably less than newer ones. For instance, list prices (government contract prices may differ from list prices) show that a combined vaccine for diphtheria, tetanus and pertussis costs ~£7 per dose compared with the new HPV vaccines which cost ~£80 a dose.[7] There is a delicate balance between achieving good value for money for the NHS, while ensuring that profit margins on older vaccines are sufficiently attractive to encourage companies to continue producing them and for new suppliers to enter the marketplace.

Security of vaccine supply

Vaccine security (uninterrupted supply of affordable vaccines) is a major strategic requirement for successful large-scale immunisation programmes. Supply can be interrupted for various reasons. For example if a vaccine is produced by only one manufacturer, then any disruption to its production such as contaminated or sub-standard product or problems with manufacturing facilities, can have a significant effect on its availability. Other manufacturers may not be able to step in to fill any gaps in supply, due to the complexities and costs of establishing and licensing plants, production processes and vaccine.

Vaccine shortages

In the US, shortages of several paediatric vaccines have been ongoing since 2000 due to a combination of factors. Several companies left the market over litigation fears. One producer stopped making tetanus and diphtheria vaccine to develop a more profitable childhood pneumococcal vaccine. This left only one other national producer, which did not have enough notice to meet the shortfall. In 2004, the MHRA suspended Chiron's manufacturing licence for its influenza plant in Liverpool due to contamination. The company was scheduled to supply ~48 million doses to the US; it did not produce vaccine for a year while addressing the problems.[8] Seasonal influenza vaccine manufacturing problems affecting the UK's supply occurred in 2005 and 2006. This did not affect the number of doses reaching patients since more than one manufacturer was supplying the DH. This illustrates how reliance on a single supplier can leave the NHS exposed, a concern raised by the House of Commons Public Accounts Select Committee in 2003.[9]

Stockpiling vaccines

DH policy aims to hold six months' worth of stock of vaccines used in national programmes at its central storage facility if there is only one supplier of a vaccine. Where there is more than one, 3 months' supply of each product is held. The benefits of stockpiling have to be carefully balanced against wastage, since vaccines have a limited shelf-life. The DH's policy of central purchase and distribution has resulted in a continuous supply of vaccines (with no shortages) for at least the last eight years for the childhood immunisation programme. Even so, the DH cannot guarantee vaccine supplies.

Vaccine manufacture and capacity

A role for public sector vaccine manufacturing?

Most European countries, including the UK, are wholly dependent on the pharmaceutical industry to supply vaccines. As a response to concerns about securing national supply of vaccines, particularly in the context of bio-terrorism or pandemic disease, the role for government-run vaccine facilities has received attention. For instance, a US Institute of Medicine report on vaccine development recommended a government-owned vaccine research and production facility to produce vaccines against emerging disease threats and bioterrorism. One parliamentary committee has questioned whether there is a need for a UK manufacturing facility that could

produce vaccines.[1] A paper by HPA officials also described a proposal for a UK facility that could develop a variety of experimental vaccines.[5] Current UK public sector vaccine manufacturing capacity is restricted to production of anthrax vaccine by the HPA.

The Netherlands (Box 5) and several Asian and Latin American countries have public sector manufacturing facilities with programmes closely tied to national health priorities. There is evidence to suggest that this can have an impact on policy by widening the choice of which vaccines to develop and use, and in securing supply.

Box 5. Public sector vaccine manufacture

Netherlands Vaccine Institute

The Netherlands Vaccine Institute is an agency of the Dutch Ministry of Health. Its core task is to guarantee the supply of vaccines for national immunisation programmes. It does this mainly by in-house production or by manufacturing vaccines under licence from pharmaceutical companies. It may also purchase vaccines from commercial suppliers.

India

The government recently closed three public sector manufacturing institutes after their licenses were suspended. A new government-run centralised vaccine technology park will replace them and is expected to be operational in 2010. This will produce the bulk of vaccines for India's national immunisation programme as well as products for export.

Experts in the UK vaccine community do not see any compelling arguments why public sector vaccine manufacture would be a good use of public money. Criticisms are that it narrows choice to less up-to-date products since national manufacturers cannot access new patented technologies and that it inhibits competition, leaving dependence on sole suppliers. They argue that public sector vaccine production in the UK would not be cost-effective and would offer few advantages over the existing arrangements.

Encouraging vaccine research

Government funded vaccine research

There is consensus that one area for improvement is in translational research (turning basic research into useful products). Early research on rotavirus was undertaken by academics and taken forward by manufacturers, leading to a new vaccine. There is some support within the vaccine community for a translational institute which could interface between research and the clinical trials/manufacturing stages.

In 2007, the Medical Research Council reviewed its vaccine research portfolio and concluded that it needed to strengthen its translational research by accelerating basic vaccine research into product development and clinical practice and using vaccine research to inform immunisation policies. Five projects have received funding, including a study to monitor the effectiveness of HPV vaccine in teenage girls.

There are some academic centres which focus on vaccine research. Some, such as the Jenner Institute in Oxford, specialise in researching novel candidate vaccines. The limiting step for such institutes is the expense of producing batches of novel vaccines and testing them in clinical trials. In 2005, in an effort to encourage UK-based pharmaceutical manufacture (including vaccines) the government invested £30m in establishing a National Biomanufacturing Centre. This facility can produce a wide variety of biopharmaceuticals (including vaccines) under contract from the private sector and academia.

Stimulating vaccine research and capacity

Recent reports have concluded that while innovative vaccine research is occurring, better co-ordinated approaches to research and development are needed. Reports have also examined availability of vaccines in general and more specifically with respect to the UK's preparedness for pandemic influenza.[1,10,11] Key recommendations to strengthen long-term strategic planning against infectious disease included:

- government investment for developing new vaccine production techniques;
- new mechanisms to encourage free exchange of proprietary technology between manufacturers;
- better incentives for the vaccine industry to develop increased global manufacturing capacity;
- reduction and streamlining of regulatory barriers for the approval of promising new vaccines.

Overview

- Vaccines are the most cost-effective health intervention.
- Vaccine development is undertaken by a handful of pharmaceutical companies and generally represents a very small part of their research portfolios.
- The UK is reliant on the international pharmaceutical sector for national vaccine supplies, which cannot be guaranteed. However there is no consensus that publicly-owned facilities would lead to better results.
- The government has to strike a fine balance between encouraging industry to develop innovative new vaccines while controlling public expenditure on them.

Endnotes

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11 *Vaccines: Innovation and Human Health*, European Academies Science Advisory Council, May 2006

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